REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-5, 7-9, 11-17 and 19-50 are in this case. Claims 38-50 have been withdrawn from further consideration, as being drawn to a non-elected invention. Claims 21-37 have been objected to. Claims 1-5, 11-17, and 19-37 have been rejected. Claims 1-5, 11-17, and 19-37 have now been amended.

This response is identical to that filed April 19, 2004, other than that the withdrawn claims are now listed herein. Applicant inadvertently had not included them in the response filed April 19, 2004.

Claims Objections

The Examiner has objected to claims 21-37 because of certain informalities.

Applicant acknowledges that although, in the previous response to official action, reference was clearly made to amendment of claim 21 to include the suggested "IVF", such amendment was unintentionally omitted from the response. Thus, claim 21 has now been amended to recite: "A method of improving in vitro fertilization (IVF) embryo implantation, the method comprising contacting an embryo generated via IVF with an effective amount of a purified recombinant heparanase...", as recommended by the Examiner.

Applicant believes to have thus overcome all claim objections.

Specification-SEQUENCE LISTING

The Specification has been amended to recite, in the aboveindicated paragraph, the amino acid sequence of human heparanase, designated herein SEQ ID NO:1, as set forth in the aboveindicated SEQUENCE LISTING. As detailed hereinbelow, SEQ ID NO:1 is identical to SEQ ID NO:10 of U.S. Patent No. 5,968,882 and SEQ ID NO:2 of PCT US99/09256 (Publication No. WO/9957244), from which the present invention derives priority, and which have been incorporated therein by reference, as indicated, for example, on page 1, lines 10-19 of the specification:

> "This is a continuation-in-part of U.S. Patent Application No. 09/260,037, filed March 2, 1999, which is a

continuation-in-part of U.S. Patent Application No. 09/140,888, filed August 27, 1998, which is a continuation-in-part of U.S. Patent Application No. 09/046,475, filed March 25, 1998, now, U.S. Patent No. 6,153,187, issued November 28, 2000, which is a continuation-in-part of U.S. Pat. application No. 08/922,170, filed September 2, 1997, now U.S. Patent No. 5,968,822, issued October 19, 1999. This application further claims the benefit of priority from U.S. Provisional Patent Application No. 60/240,037, filed October 17, 2000. The specifications of the above-cited applications are incorporated herein by reference."

on page 13, lines 25-30:

"Further details pertaining to heparanase, heparanase gene and their uses can be found in, for example, PCT/US99/09256; PCT/US98/17954; PCT/US99/09255; PCT/US99/25451; PCT/IL00/00358; PCT/US99/15643; PCT/US00/03542; and PCT/US99/06189; and in U.S. Patent Nos. 6,242,238; 5,968,822; 6,153,187; 6,177,545; and 6,190,875, the contents of which are hereby incorporated by reference."

and on page 18, line 30, to page 19, line 4:

"The heparanase can be natural (purified) or recombinant and optionally modified, precursor (e.g., pro-heparanase or pre-pro-heparanase) or activated (e.g., mature heparanase) form, as described in, for example, PCT/US98/17954 and PCT/US99/09256, which are incorporated herein by reference."

Specifically, PCT US99/09256 (Publication No. WO/9957244), incorporated in the instant application as detailed hereinabove, teaches:

"The functional part may be either man induced by genetic engineering or post translation artificial processing (e.g., by a protease) or naturally processed, depending on the cellular system employed.

According to another preferred embodiment of the present invention, the polypeptide includes an amino acid sequence as set forth in SEQ ID NO:2 or a functional part thereof having heparanase catalytic activity. However, the scope of the present invention is not limited to SEQ ID NO:2 or a functional part thereof, as natural and man made innocuous variations thereof (e.g., mutations, such single amino acid substitution) may also have heparanase catalytic activity. Polypeptides corresponding to species other than human and having heparanase catalytic activity are also within the scope of the present invention."(page 31, lines 15-28)"

Wherein SEQ ID NO:2 of PCT US99/09256, and SEQ ID NO:10 of US Patent No. 5,968,882 is the sequence of human heparanase, 543 amino acids in length, identical to the sequence in GenBank Accession No. NP 006656.

Support for the limitation of at least 95% homology to human heparanase is found in the instant specification, as cited above:

""The heparanase can be natural (purified) or recombinant and optionally modified, precursor (e.g., pro-heparanase or pre-pro-heparanase) or activated (e.g., mature heparanase) form, as described in, for example, PCT/US98/17954 and PCT/US99/09256, which are incorporated herein by reference."(page 18, line 30, to page 19, line 4)

In this regard, US Patent Application No. 5,968,822, from which the present application derives priority (see above) also specifically recites a heparanase polypeptide having a range of homology to human heparanase:

> "...any polynucleotide sequence which encodes a polypeptide having heparanase activity, which shares at least 60% homology, preferably at least 70% homology, more preferably at least 80% homology, most preferably at least 90% homology with SEQ ID NO:10 is within the scope of the present invention."

Wherein SEQ ID NO:10 of US Patent No. 5,968,822 is identical to now amended SEQ ID NO:1 of the instant invention, recited in now amended claim 1.

Thus, the limitation of 95% homology included in now amended claim 1 clearly falls within the range of homology to human heparanase polypeptide taught in the specifications of the incorporated, issued parent patents.

Thus, the introduction of the above-indicated amendments to the specification does not constitute new matter and serves to further clarify and define the present invention, without introducing new material.

Computer Readable Format

It is hereby declared that in accordance with the requirements of 37 CFR 1.821, a copy of the abovementioned SEQUENCE LISTING in Computer Readable Format is enclosed, identical to the print copy provided herein.

Thus, the introduction of this amendment to the specification does not constitute new matter and serves to further clarify and define the present invention, without introducing new material.

35 U.S.C. § 112 First Paragraph Rejections

The Examiner has rejected claims 1-5, 7-9, 11-17 and 19-37 under 35 U.S.C. § 112, First Paragraph, as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors, at the time that the application was filed, had possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 1-5, 7-9, 11-17 and 19-37 have now been amended.

The Examiner has rejected the arguments presented in the previous response to the Official Action (dated August 4, 2003). The Examiner states that the claimed

methods of improving embryo implantation recite any mammalian heparanase, while the specification only provides a method of improving embryo implantation with "CHO-p65" heparanse, as stated in the Official Action mailed April 8, 2003. The Examiner further states that the recitation, in amended claims, of "mammalian heparanase" lacks support in the original specification.

Applicant wishes to reemphasize that, as detailed in the previous official action, heparanases purified from different human and animal sources not only have similar endo-β-N-glycosidase catalytic activity, share similar substrate specificities, yield similar oligosaccharide cleavage products and are similarly inhibited by heparin substrate derivatives, but have also been shown to have structural similarity. Thus, one of ordinary skill in the art would readily recognize that any mammalian heparanase, even of diverse origins, having an endo-β-N-glycosidase catalytic activity, is suitable for the methods of the present invention.

The abovementioned notwithstanding, in order to expedite prosecution, Applicant has chosen to amend claims 1,21, 26 and 31 to include the limitation:

> "...effective amount of a purified recombinant heparanase at least 95% homologous to SEQ ID NO:1."

thus limiting the heparanases recited in independent claims 1, 21, 26 and 31 to heparanase polypeptides having exceedingly high homology to human heparanase, as is described in detail in the instant specification. Support for such an amendment is found throughout the instant specification, for example, in page 18, line 26 to page 19, line 21:

> "As used herein the term "heparanase" refers to an animal endoglycosidase hydrolyzing enzyme which is specific for heparin or heparan sulfate proteoglycan substrates, as opposed to the activity of bacterial enzymes (heparinase I, II and III) which degrade heparin or heparan sulfate by means of β-elimination. The heparanase can be natural (purified) or recombinant and optionally modified, precursor (e.g., pro-heparanase or pre-pro-heparanase) or activated (e.g., mature heparanase) form, as described in, for example, PCT/US98/17954 and PCT/US99/09256, which are

incorporated herein by reference."

"For different applications, the...source of heparanase used may vary."

"As used herein in the specification and in the claims section below, the term "purified" includes also enriched. Methods of purification/enrichment of heparanase are well known in the art. Examples are provided in U.S. Pat. Application No. 09/071,618, filed May 1, 1998, in Goshe R *et al.* Mol. Human Reprod. 2, 679-684, 1996 and in WO91/02977, which are incorporated herein by reference."

"As used herein the term "recombinant" refers to an enzyme produced via genetic engineering techniques."

"As used herein in the specification and in the claims section below, any enzyme, such as heparanase, refers both to the inactive pro-enzyme form and to its processed active form."

Further support for such an amendment is found in U.S. Patent Nos. 6,242,238; 5,968,822; 6,153,187; 6,177,545; and 6,190,875, the contents of which have been fully incorporated into the instant specification by reference (see page 13, lines 25-30). For example, PCT US99/09256 (Publication No. WO/9957244), which has been incorporated in the instant application by reference, teaches:

"The functional part may be either man induced by genetic engineering or post translation artificial processing (e.g., by a protease) or naturally processed, depending on the cellular system employed.

According to another preferred embodiment of the present invention, the polypeptide includes an amino acid sequence as set forth in SEQ ID NO:2 or a functional part thereof having heparanase catalytic activity. However, the scope of the present invention is not limited to SEQ ID NO:2 or a functional part thereof, as natural and man made innocuous variations thereof (e.g., mutations, such single

> amino acid substitution) may also have heparanase catalytic activity. Polypeptides corresponding to species other than human and having heparanase catalytic activity are also within the scope of the present invention."(page 31, lines 15-28)

Wherein SEQ ID NO:2 is the sequence of human heparanase, 543 amino acids in length, identical to the sequence in GenBank Accession No. NP 006656. Applicant wishes to further point out that the abovementioned SEQ ID NO:2 is identical to the now introduced SEQ ID NO:1, which is recited in now amended claim 1. US Patent Application No. 5,968,822, from which the present application also derives priority (see above) also specifically recites a heparanase polypeptide having a range of homology to human heparanase:

> "...any polynucleotide sequence which encodes a polypeptide having heparanase activity, which shares at least 60% homology, preferably at least 70% homology, more preferably at least 80% homology, most preferably at least 90% homology with SEQ ID NO:10 is within the scope of the present invention."

Wherein SEQ ID NO:10 of US Patent No. 5,968,822 is identical to now amended SEQ ID NO:1 of the instant invention, recited in now amended claims 1, 7, 13, 21, 26 and 31.

Thus, the limitation of 95% homology included in now amended claim 1 clearly falls within the range of homology to human heparanase polypeptide taught in the specifications of the incorporated, issued parent patents.

Further support for the limitation of 95% homology can be found in the comparison of catalytically identical heparanase homologues of different species, as described hereinabove. As described in the attached Appendix A (which is alignment data taken from an affidavit that was submitted in another application by the same inventors, US Serial Number 09/988,113, Attorney Docket No. 01/22781), heparanase from mouse has a homology of 70% to human heparanase, while heparanase from chick only has a homology of 60% to human heparanase. Yet these heparanase proteins are still clearly, recognizably heparanase, they retain heparanase functionality

and they have a similar level of activity, in comparison to human heparanase. Thus, clearly heparanase proteins featuring a sequence of at least 95% homology to human heparanase are well within the level of homology that could be expected for heparanase, and that would result in a protein that has heparanase activity.

Further, Applicant would like to point out that the submitted alignment data in attached Appendix A, showing the homology (and differences) between human, rat, mouse and chicken heparanase sequences, including some important shared features such as the heparan-sulfate binding site (marked), further supports Applicant's statements with regard to the ability of one of ordinary skill in the art to readily recognize a heparanase protein as such. Furthermore, Applicant again notes that such homology can even be detected in a heparanase protein that has sequence homology of less than 70%; while for the present invention claims recite "at least 95%" homology. Thus, Applicant has limited the recited homology even greater than that which could be predicted for heparanase proteins, based upon the large amount of information that is available about other members of the heparanase family.

Similarly, support for the use of purified recombinant heparanase in the methods of the present invention is found throughout the instant specification, for example:

> "CHO-p65 heparanase (1.693 mg/ml; Batch No. 11-1) was used in all experiments performed. CHO-p65 heparanase was prepared according to the protocol described in WO 01/7297."(page 26, lines 12-14)"

As detailed in the previous response to Official Action, the "CHO-p65 heparanase" is recombinant human heparanase expressed in Chinese Hamster Ovary cells (for details, see US Patent Application No. 09/071,618, which has been incorporated into the instant specification by reference), identical in amino acid sequence, substrate specificity, kinetic characteristics catalytic activity, and antigenicity to an active heparanase enzyme characteristic of human tissues, having high homology to heparanase of other mammalians, such as SEQ ID NO:1 recited in amended claims 1, 7, 13, 21, 26 and 31.

Methods for purification of heparanse are also described:

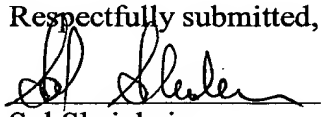
> "As used herein in the specification and in the claims section below, the term "purified" includes also enriched. Methods of purification/enrichment of extracellular matrix degrading enzyme are well known in the art. Examples are provided in U.S. Pat. Application No. 09/071,618, filed May 1, 1998, in Goshen et al. [Goshen R *et al.* Mol. Human Reprod. 2, 679-684, 1996] and in WO91/02977, which are incorporated herein by reference."(page 19, lines 9-14).

Thus, claims 1, 7, 13, 21, 26 and 31 as now amended, and all claims directly or indirectly dependent therefrom, now describe the claimed invention in full, clear concise and exact terms that a skilled artisan would recognize, thus enabling one of ordinary skill in the art to make and use the claimed methods, without requiring undue, improper or extensive experimentation.

In view of the amendments and objective evidence presented hereinabove, the Applicant believes to have overcome the 35, U.S.C 112, first paragraph, rejections.

In view of the above amendments and remarks it is respectfully submitted that now amended independent claims 1, 7, 13, 21, 26 and 31 and claims 2-5, 8, 9, 11, 12, 14-17, 19, 20, 22-25, 27-30 and 32-37 directly or indirectly depending therefrom are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



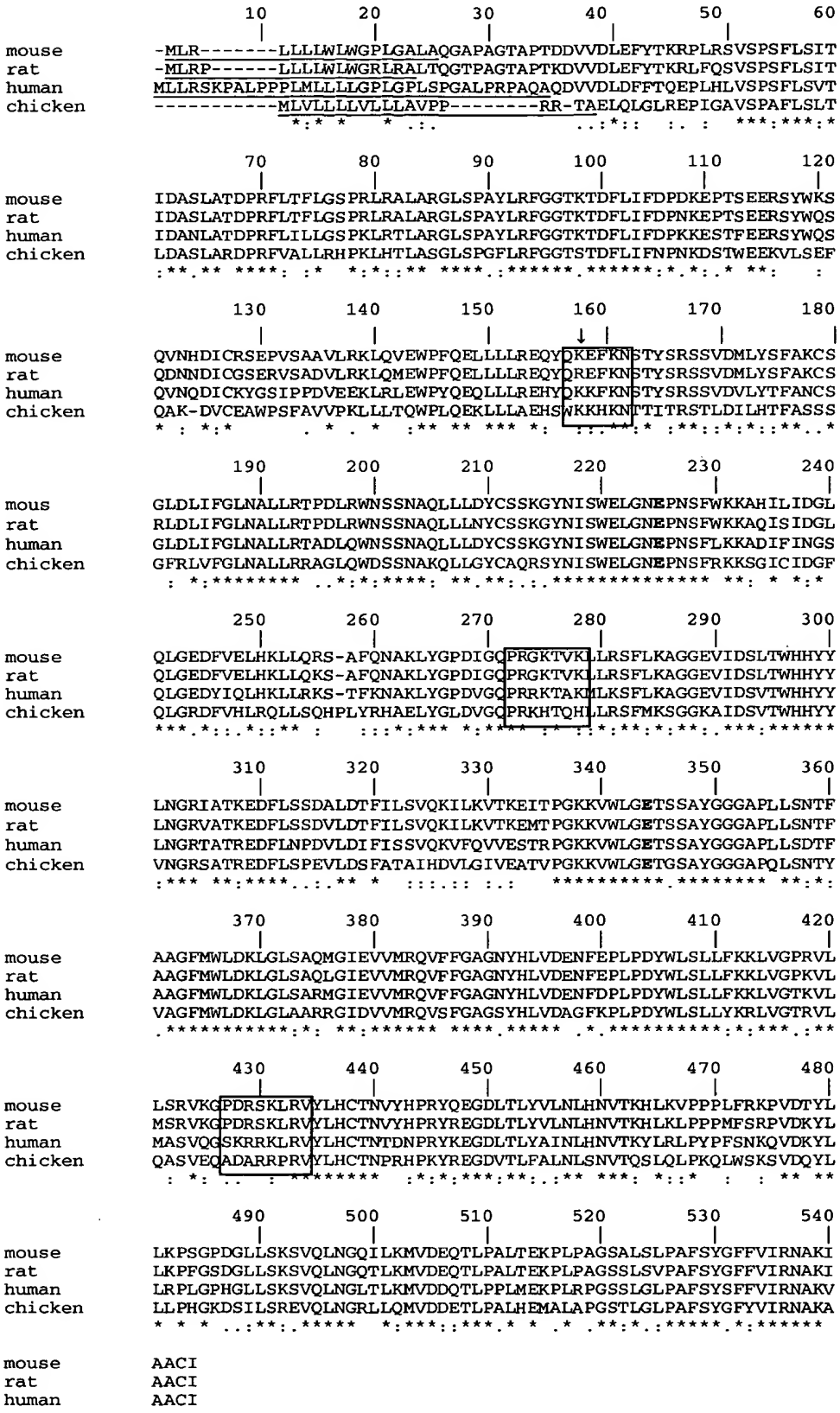
Sol Sheinbein
Registration No. 25,457

Date: May 17, 2004

Enclosed:

SEQUENCE LISTING in computer readable format
Appendix A

APPENDIX A- Heparanase Sequence Homology Data



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chicken         IACI
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Multiple alignment of heparanase from Human, Rat, Mouse and chicken generated by Clustal W. Active site residues are bolded and putative heparin binding sites are boxed.